NEUROMA EMBRYONALE OF THE CHOROID PLEXUS OF THE CAT.

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Plates IX and X.

The examination of the tumor which I am describing was made at the request of Dr. Frank P. Knowlton, who described the physiological features of the animal at the meeting of the American Physiological Society in Philadelphia, December, 1904.

In 1904, Verhoeff[1] described a rare tumor (terato-neuroma) arising from the Pars ciliaris retinæ. He regarded it as of a nature hitherto unrecognized and he discussed its relation to so-called Glioma retinæ. The primary and secondary optic vesicles, embryonic retina, and vitreous humor and the hyaloid membrane were represented in the tumor. Verhoeff thought that the term "terato-neuroma" would seem to express well the general characters of the tumor, indicating as it does a monster-like growth composed of nervous elements, and that the term has the advantage of being applicable to tumors of similar nature which possibly may arise elsewhere in the nervous system.

I shall describe in this paper a tumor of the cat, probably arising in the choroid plexus, which may belong to the same class. In its essential features this tumor appears to represent the central nervous system, although in an atypical and an early embryonic stage, previous to the differentiation of neuroblasts. In a personal communication Verhoeff, who has examined sections of my tumor, suggests the name "Neuroma embryonale" as applicable to both tumors.

The tumor in the cat was situated in the fourth ventricle. In the region of its greatest diameter it occupied the left half of the floor of the ventricle, extending from the median line to

[1] *Trans. of the Am. Ophthal. Soc.*, 1904, x, 351.

the Corpus restiforme. Anteriorly and posteriorly it lay in the depth of the tissue to the ventral side of the ventricle. It was approximately spherical in form and measured in its greatest diameter nine millimeters. The center of the tumor was converted into a large cyst about which the tumor tissue formed a thin wall. In a cross-section of the tumor and surrounding structures a marked disturbance of the internal relations of the medulla and, to a less extent, of the cerebellum was apparent. This was due to the infiltrative growth of the tumor into the tissue, as proven also by the microscopical examination. The tumor consists of tissue resembling the central nervous system in an early stage of development. It shows numerous lumina, in section circular or elongated in form, corresponding to the embryonic neural canal. An inconspicuous mesenchymal framework is present. There is no mesenchymal capsule.

Microscopical examination of the formalin-hardened tumor was made. The Benda method for staining neuroglia fibrils as employed by Huber [2] was used, except that the chloroform method of embedding in paraffin was substituted. Specimens were also stained with hæmatoxylin and eosin, and by Van Gieson's method.

The entire growth is uniform in character. A condition such as that seen in Fig. 4 suggests an early stage of the neural tube, consisting of a single layer of cells or spongioblasts. The cells are not completely isolated from each other so that the tissue is distinctly syncytial in character. The free ends of the cells project through the Membrana limitans epithelii.[3] In Fig. 2 from

[2] Huber, "Studies on the Neuroglia," *Am. Jour. Anat.*, 1901, i, 45.

[3] Dr. Verhoeff proposes this name for the membrane described by him ("A Hitherto Undescribed Membrane of the Eye, and its Significance," *Royal London Ophthal. Hosp. Reports*, 1903, xv, 309), and through his generosity I am permitted to introduce it here. He has also published further observations on the membrane ("The Mixed Tumors of the Lachrymal and Salivary Glands," *Jour. of Med. Research*, 1905, xiii, 319). It is described as a fenestrated membrane, occurring also in the ependyma of the central nervous system, and is compared to a wire screen with hexagonal openings, the latter corresponding in size to the cross-sections of the cells. It corresponds, no doubt, to what is frequently described as the Membrana limitans interna or as a cuticular surface. When seen in cross-section, the membrane gives the appearance of a sharp internal margin to the cells. When seen in plane-section its fenestrated structure is

another part, a later stage of the nervous system is represented in the tumor. The cell boundaries in this part are still less distinct and the neurospongium of His appears to have formed. The dividing nucleus in the internal border zone corresponds to a germinal cell of His. Along the mesenchyma the protoplasm forms a continuous layer corresponding to the Margo limitans. This layer is seen in the figure along two sides, but in some cases, where the tube is seen in section to be completely surrounded with mesenchyma, the picture is even more suggestive of the normal neural tube with its embryonic membranes. The space separating the two represents, perhaps, the epicerebral lymph space, but it is not to be excluded that this appearance may be due to the fixing reagent.

In Fig. 1 a portion of the wall of a tube in a still later stage of development is represented. A section of a blood-vessel corresponding to those which penetrate the normal neural tube at this stage is also to be seen. The Margo limitans is developed about the vessel. The Margo limitans is seen especially well developed below the vessel in the figure, and it appears widely separated from the vessel wall by a space across which pass slender strands of tissue.

The nuclei appear large, vesicular, and round or oval in sections. In the tissues fixed in formalin they have a well-marked chromatin network. The nuclear membrane is distinct and large nucleoli are present (Figs. 1, 2, 3, and 4). In sections stained with hæmatoxylin and eosin the nucleoli appear refractile and translucent (Fig. 1), while with the Benda method they stain intensely black (Figs. 2, 3, and 4). The long axes of the nuclei are usually arranged radially to the lumina. The tissue in the sections appears never to reach a stage where mitosis ceases, and hence mitotic figures are found more or less frequently throughout.

Where the tissue shows later stages of development the sec-

apparent. In the embryonic nervous system the ependymal dots described by Weigert in adult ependyma, where many of them occur in each cell, are arranged in pairs, two occurring in each cell on a level with the fenestrated membrane and in the center of each of its openings.

tions stained by Benda's method show a few neuroglia fibrils, usually at a considerable distance from the lumina. They appear to have the same relation to cells as in normal neuroglia. Nothing corresponding to neuroblasts is seen. Thus a differentiation leading to the formation of neuroglia only, takes place in certain regions.

In serial sections independent lumina can be followed throughout their entire extent. One of the smaller lumina (Fig. 4) is eight microns in diameter measured from the Membrana fenestrata epithelii. The latter membrane is well defined and is seen as a sharp line. The appearance of processes passing out from the membrane between the cells results from the screen-like structure of the membrane. The protoplasm of the spongioblasts appears to project as a continuous mass through the membrane into the lumen. This lumen is evident in only three sections of the series.

It may be that the origin of the lumina is the same as the origin of the lumen in a solid anlage of the nervous system, as in the teleostei. Lumina of intermediate sizes between the smallest and largest are encountered.

Verhoeff speaks in the following way of the possible part played by the Membrana fenestrata epithelii in the development of the lumina in the so-called Glioma retinæ: "The structure of the membrane in the rosettes explains why the latter assume their peculiar form, for it is evident that if a few cells became bound together by such a membrane, and they were otherwise unhampered in their growth, they would be compelled to form a more or less spherical body. If the free ends of the cell groups did not finally meet, a spiral figure would result, and just such spirals are frequently seen. The writer has also found single cells with a membrane on one end, as well as curved groups of several cells which were obviously the beginnings of rosettes. This explains very well why tumor cells are often seen within the cavity of rosettes, evidently being enclosed during the formation of the latter." This method of formation would explain the presence of tumor cells in the lumina in the present case also, but the spiral figures are not met with. Ribbert, in

describing the lumina sometimes occurring in gliomata, notes that some lumina appear to be surrounded with radially arranged cells in only a part of their circumference.[4] The appearance would seem sometimes at least to result from irregularities in the form of the lumina. As a result of this the ependymal layer is cut tangentially in a part of the circumference, and so does not present its best known appearance. In my case, possibly, the membrane has had a more or less spherical arrangement from the time of its origin, the cells in the interior gradually undergoing degeneration and disappearing, but the method of formation of the lumina was not determined.

In Fig. 2 the Membrana fenestrata epithelii is seen to be well defined about a considerable portion of the lumen. Processes of the cells project through it into the lumen. Tumor cells are present in the lumen, a condition which is seen frequently. The protoplasm of these cells appears to have undergone degeneration, staining relatively deeply. The nuclei usually are more or less indistinct. The protoplasm frequently is continuous with the processes of the cells extending into the lumen. The condition, such as that presented in this figure, suggests that cells in the internal border zone, instead of migrating peripherally, may sometimes migrate into the lumina, and then, on account of unfavorable nutritive conditions, gradually undergo degeneration.

In sections tangential to the lumina and passing between the Membrana fenestrata epithelii and the nuclei a further study of the form of the "columnar cells" may be made. The tissue is seen to consist of a syncytium in which there are large spaces (Fig. 3). These spaces correspond to those which, in sections passing through the center of lumina, appear to separate individual "columnar cells" from each other.

The tissue appears to be arranged symmetrically about the lumina in every direction. Nothing corresponding to the dorso-ventral axis of the developing nervous system is seen. The elongated form of some of the lumina suggests a representation of the antero-posterior axis. Sometimes the tubes are folded in a way resembling the folding of the normal neural tube in the

[4] Ribbert, *Geschwulstlehre*, 1904, 336.

development of the various territories of the central nervous system.

In sections tangential to the lumina a study of the Membrana fenestrata epithelii may be made. Pictures corresponding exactly, as far as the membrane and ependymal dots are concerned, to those given in the description of the tumor of the Pars ciliaris, are seen. Where the section passes near the periphery of the lumen the membrane is seen both in cross- and plane-section. The membrane appears to be present in connection with the smallest lumina.

The method of growth of the mesenchymal framework is not evident. No active proliferative process is seen in it. The larger vessels are surrounded by a cellular adventitial sheath which is closely applied to the wall of the vessel and frequently is separated by a wide space from the surrounding epithelium. Often, however, the epithelium is closely applied to the mesenchymal tissue, in which case no evidence of the perivascular space exists.

Origin of the Tumor.—In the region of the fourth ventricle the cells which would seem most likely to possess the potentiality for the formation of the entire nervous system are the epithelial cells lining the choroid plexus. Morphologically, also, they correspond most nearly to the original epithelial cells of the medullary plate and the neural tube. Such an origin would correspond to the origin of the tumor of the Pars ciliaris retinæ, from the unpigmented epithelium of the retina. In sections the epithelium of the choroid plexus may be traced into direct continuity with tumor cells, and transitional forms between the two appear to occur. Pictures are seen corresponding to Fig. 2 in Verhoeff's description, which shows the tumor cells in continuity with the unpigmented epithelium.

In the case of the tumor of the Pars ciliaris it seems probable that the original process was one of resumption by the unpigmented epithelium of properties leading to the formation of the primary and secondary optic vesicles (Verhoeff's Figs. 2 and 8). The condition of the cells in these figures corresponds more or less to those present in my Fig. 4. The lumina in Verhoeff's

tumor arise as the result of a convoluted papillary outgrowth of the epithelium and the underlying stroma. The "second type of convolution," representing the early embryonic retina (Verhoeff's Fig. 6), corresponds most nearly to that shown by my Fig. 2.

In the case of the tumor of the choroid plexus of the cat the epithelium lining the plexus appears to have resumed, although atypically, the properties of the epithelium of the embryonic neural tube.

It may be objected that if the tumor is to be regarded as a neuroma there should be evidence of the formation of neuroblasts. But the tissue may be regarded as in a stage of development anterior to the appearance of these cells. Moreover, there are territories in the lining of the neural tube aside from the one giving rise to the choroid plexus, that give origin only to neuroglia and not at all to nervous elements. This is true, for example, of the territories from which the optic nerves originate. The epithelial cells give rise simply to the neuroglia framework of the nerves which supports the fibers of the nerve cells originating at another level. Yet these cells probably possess the potentiality for the formation of neuroblasts. Perhaps some tumors described as ependymal gliomata belong in the same class with this tumor.

For the drawings of Figs. 2, 3, and 4 I am indebted to Dr. Francis A. Hulst.

EXPLANATION OF PLATES IX AND X.

In all the figures the outlines were drawn with the aid of the Abbe camera lucida (Leitz Obj. 7, Oc. 5), and the detail is added with higher magnification (Leitz Obj. $\frac{1}{12}$, Oc. 5). The drawings, except Fig. 1, are all slightly reduced.

Fig. 1.—A part of the wall of a relatively large tube. Hæmatoxylin and eosin staining.

Fig. 2.—Medium size tube showing the Margo limitans on two sides. The appearance resembles the cross-section of the embryonic neural tube. The stroma is shown to the right and below. Benda's neuroglia fibril stain.

Fig. 3.—Section tangential to a lumen between the Membrana fenestrata epithelii and the nuclei. The relatively deeply staining area of protoplasm in the center of the figure is found in neighboring sections of the series to be associated with a mitotic nucleus. Small amount of stroma shown in lower right-hand corner. Benda's neuroglia fibril stain.

Fig. 4.—Section through the center of one of smaller tubes. The appearance similar to that of the neural tube consisting of one layer of cells. Benda's stain.

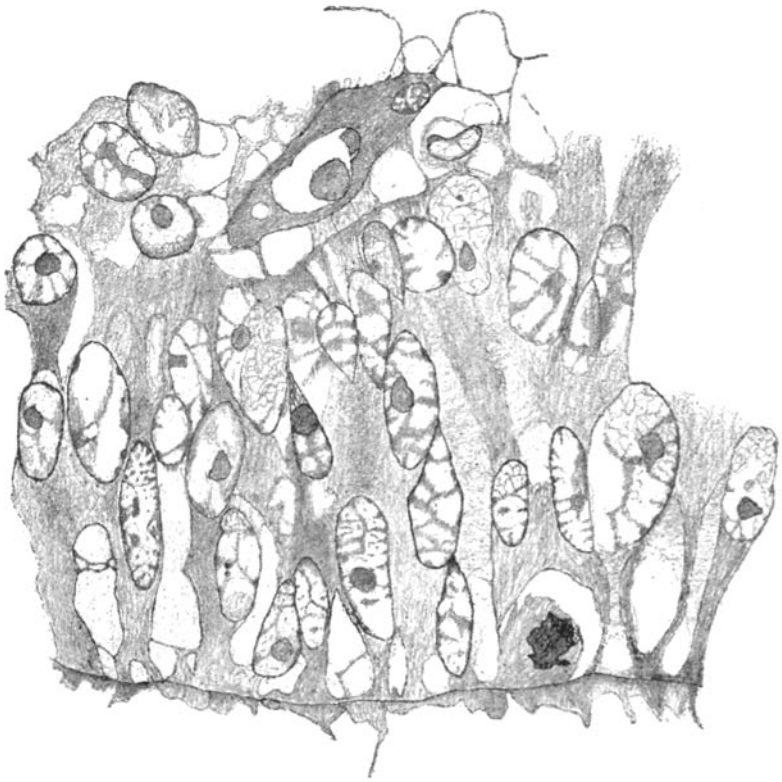

FIG. 1

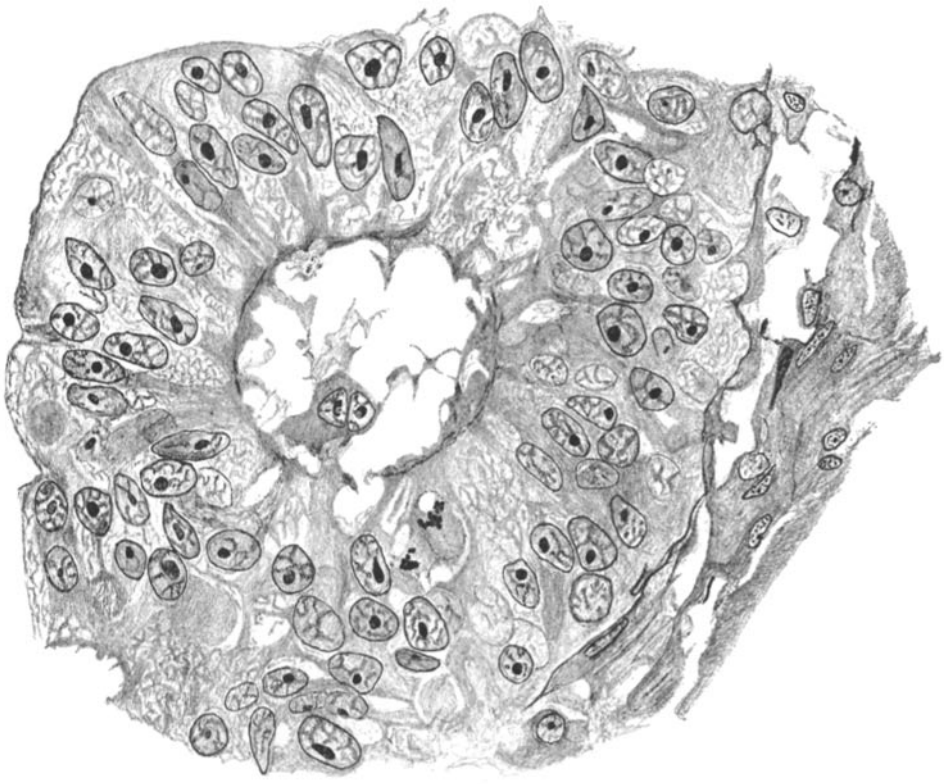

FIG. 2

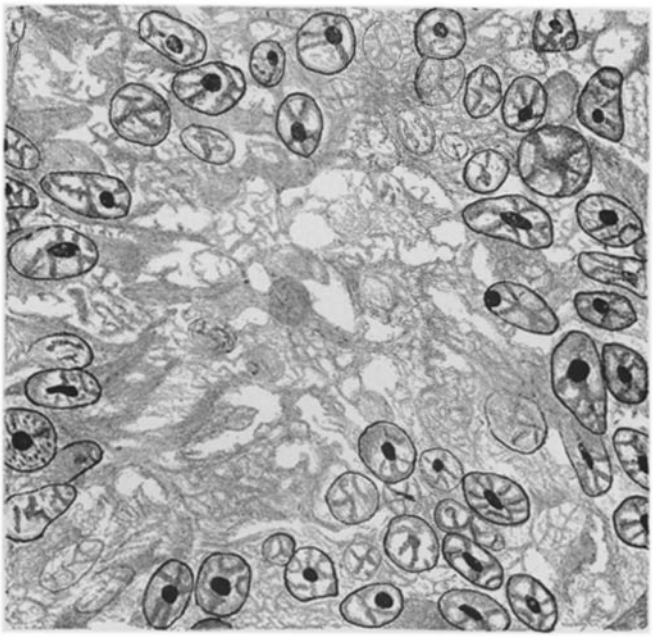

FIG. 3

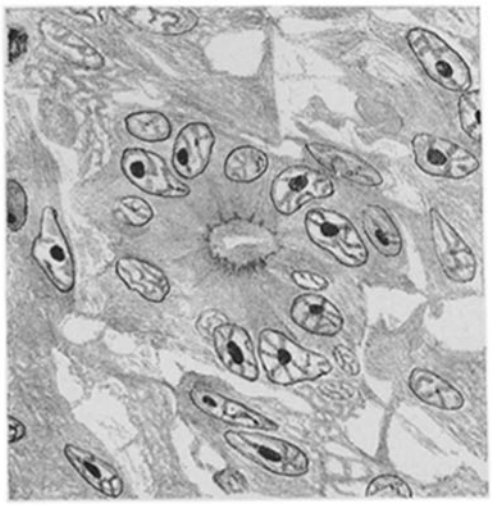

FIG. 4